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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,546	09/20/2001	Omolayo O. Famodu	BB-1324	1565

7590 01/06/2004

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EXAMINER	
BUI, PHUONG T	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M. SM

Office Action Summary	Application No.	Applicant(s)	
	09/868,546	FAMODU ET AL.	
	Examin r	Art Unit	
	Phuong T. Bui	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/14/03 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 25-37 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 25-37 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 01242002 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Office acknowledges the receipt of Applicant's restriction election filed July 14, 2003. Applicant elects Group I and Group A (SEQ ID NO:1 encoding SEQ ID NO:2) without traverse. Claims 25-37 are pending and are examined in the instant application. This restriction is made FINAL.

Sequence Listing

2. Applicant's CRF and paper sequence listing have been entered. However, upon examination of SEQ ID NO:1 and its corresponding amino acid sequence SEQ ID NO:2, it is unclear what region of SEQ ID NO:1 encodes SEQ ID NO:2. Clarification is required.

Information Disclosure Statement

3. An initialed and dated copy of Applicant's IDS form 1449, filed January 24, 2002, is attached to the instant Office action.

Claim Rejections - 35 USC § 101 Utility

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-37 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility. First of all, Applicant asserted that the nucleotide sequence SEQ ID NO:1 encoding SEQ ID NO:2 has isoflavone 2-hydroxylase protein activity. However, SEQ ID NO:1 does not appear to encode a complete protein, as the first amino acid is a leucine and not a methionine –

a methionine may indicate it is the encoded initiation codon. Applicant does not indicate where the reading frame for SEQ ID NO:1 encoding SEQ ID NO:2 begins or ends (see "Sequence Listing" section above). Applicant provided no evidence that SEQ ID NO:2 has the asserted activity. It is then unclear as to whether SEQ ID NO:1 is only a partial sequence of the isoflavone 2-hydroxylase and does not have isoflavone 2-hydroxylase activity.

Secondly, Applicant's functional assignment for the encoded protein of SEQ ID NO:2 is based solely upon sequence alignment with a single prior art sequence. Neither Applicant's disclosure nor the state of the prior art at the time the invention was made provides guidance as to where the catalytic domain for Applicant's protein activity is located. Applicant provided no empirical data to verify that SEQ ID NO:1 encodes a polypeptide having isoflavone 2-hydroxylase activity, i.e., containing the catalytic domain. In Table 4 of the specification, Applicant indicates that SEQ ID NO:2 has 60% sequence identity to a prior art isoflavone 2-hydroxylase protein. However, since SEQ ID NO:2 is a partial protein sequence, it is unclear what percent sequence identity the entire protein containing SEQ ID NO:2 would have with the entire protein of the prior art isoflavone 2-hydroxylase. It is also unclear that the prior art isoflavone 2-hydroxylase used by Applicant for sequence comparison is a complete protein, as such was not disclosed by Applicant. The state of the art to date does not recognize that a 60% sequence identity of a partial protein with another protein is sufficient for predicting protein function, especially without any disclosure as to how large the protein is, what size variations exist within the genus of isoflavone 2-hydroxylases, whether or not there

are highly conserved regions between the different species of isoflavone 2-hydroxylases, where the functional domains are, and most importantly, whether or not SEQ ID NO:2 contains all the highly conserved regions and functional domains necessary for isoflavone 2-hydroxylase activity. Without such activity, SEQ ID NO:1 or a polynucleotide sequence encoding SEQ ID NO:2 would lack (asserted) utility.

Thirdly, sequence alignment allows one skilled in the art to predict or assign a tentative functional alignment. It does not replace empirical data and is not a verification of a functional activity of a protein. Bork (Genome Research, Vol. 10, 2000, p. 398-400 (U)) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col. 1). One of the reasons for this inaccuracy is that the quality of data in public databases is still insufficient. This is particularly true for data relating to protein function. Protein function is context dependent, and both molecular and cellular aspects must be considered (p. 398, col. 2). Conclusions from comparison analyses are often stretched with regard to protein products (p. 398, col. 3). Furthermore, although gene annotation via sequence database searches is already routine, even here the error rate is considerable (p. 399, col. 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply certain functionality (see p. 399, Table 1 legend). As more sequences are added to databases and as errors accumulate and propagate, it

becomes more difficult to infer correct function from the many possibilities revealed by a database search (p. 399, paragraph spanning cols. 2 and 3). Bork cautions that, although current methods seem to capture important features and define general trends, 30% of structure-function features are missing or predicted inaccurately. This must be kept in mind when processing the results (p. 400, paragraph spanning cols. 1 and 2). Moreover, Lazar et al. (Molecular and Cellular Biology, March 1988, Vol. 8, No. 3, p. 1247-1252 (V)) teaches a mutation of aspartic acid 47 and leucine 48 of a transforming growth factor results in different biological activities (Title). Burgess et al. (The Journal of Cell Biology, 1990, Vol. 111, p. 2129-2138 (W)) teaches a single mutation at position 132 from lysine to a glutamic acid residue causes possible dissociation of the heparin-binding and mitogenic activities of heparin-binding (acidic fibroblast) growth factor-1 from its receptor-binding activities (Abstract). Broun et al. (Science, 13 November 1998, Vol. 282, p. 131-133 (X)) teaches as few as four amino acid substitutions can convert an oleate 12-desaturase to a hydroxylase and as few as six result in conversion of a hydroxylase to a desaturase (Abstract). Based upon the teachings of these references, the state of the art recognizes that a single or very few amino acid differences can alter or ablate protein activity, and a 60% sequence identity with a prior art isoflavone 2-hydroxylase does not allow one skilled in the art cannot conclude that a partial protein of SEQ ID NO:2 has isoflavone 2-hydroxylase activity. While Applicant is not required to provide empirical data to verify the asserted protein activity of Applicant's SEQ ID NO:2, given (a) the fact that SEQ ID NO:1 encodes a partial protein; (b) the lack of verification of isoflavone 2-hydroxylase activity" for SEQ ID

NO:2; (c) the lack of guidance as to whether or not SEQ ID NO:2 possesses the catalytic domain essential isoflavone 2-hydroxylase activity; (d) the fact that Applicant used solely sequence alignment to predict function; (e) the 60% sequence identity partial protein SEQ ID NO:2 has with the closest prior art isoflavone 2-hydroxylase; and (e) the negative teachings of Bork, Lazar, Burgess and Broun above, one skilled in the art cannot reasonably conclude that SEQ ID NO:2 has the asserted isoflavone 2-hydroxylase activity or has utility under current utility guidelines.

In addressing claims drawn to a sequence having 80- 95% sequence identity at the amino acid level to a nucleotide sequence encoding SEQ ID NO:2, since SEQ ID NO:1 and a polynucleotide encoding SEQ ID NO:2 lack utility for the reasons set forth above, sequences having less than 100% sequence identity would also lack utility. Applicant should note that no working examples of a sequence having 80-95% sequence identity having isoflavone 2-hydroxylase activity are set forth in Applicant's disclosure.

Additionally, there also is no well-established utility for SEQ ID NO:1 and a sequence encoding SEQ ID NO:2. SEQ ID NO:1 does not have a well-established utility for hybridization purposes because the encoded protein does not have utility for the reasons indicated above. Furthermore, a polynucleotide encoding SEQ ID NO:2, (at 80% sequence identity at the amino acid level) would not necessarily hybridize to SEQ ID NO:1 due to codon degeneracy. Thus, for the reasons set forth, the claimed invention lacks utility under current utility guidelines. (see Utility Examination Guidelines

published in Federal Register/ Vol. 66, No. 4/ Friday, January 5, 2001/ Notices; p. 1092-1099).

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 25-37 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Furthermore, in addressing claims reciting percent sequence identity, because Applicant does not teach which regions of SEQ ID NO:1 or a sequence encoding SEQ ID NO:2 should be retained and which would tolerate unspecified additions, deletions, and/or substitutions, one skilled in the art would not be able to make and use the claimed invention without undue experimentation. While one skilled in the art can readily make all such changes, further guidance is needed as to what changes one could make and retain activity. As discussed in the utility rejection above, one or very few amino acid changes can ablate or alter protein activity and function. Thus, given the lack of guidance, lack of working examples, breadth of the claims of the 80-95% sequence identity sequences, and unpredictability as to what changes would retain enzyme activity, Applicant has not fully enabled the invention as commensurate in scope with the claims.

6. Claims 25-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. The claims reciting 80-95% sequence identity lack adequate written description because Applicant does not disclose a representative number of species as encompassed by these claims. The claims encompass mutants and allelic variants and thus imply that structural variants exist in nature, yet no structural variant has been disclosed. The claims also encompass isoflavone 2-hydroxylase from other species. The implication is that there is a gene and a protein other than that disclosed which exists in nature, but the structure thereof is not known. Applicant discloses a single sequence SEQ ID NO:1 isolated from *Glycine max*. Thus, there is insufficient relevant identifying characteristics to allow one skilled in the art to predictably determine such mutants, allelic variants and isoflavone 2-hydroxylases from other plants and organisms, absent further guidance. Accordingly, there is lack of adequate description to inform a skilled artisan that applicant was in possession of the claimed invention at the time of filing. See Written Description guidelines published in Federal Register/ Vol.66, No. 4/ Friday, January 5, 2001/ Notices; p. 1099-1111.

Remarks

7. No claim is allowed. SEQ ID Nos. 1 and 2 are free of the prior art. It is understood by the Office that the Clustal method of alignment of sequences uses the default parameters set forth on page 7 of the specification.

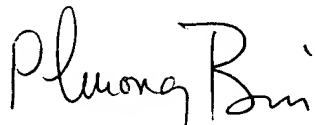
8. Papers relating to this application may be submitted to Technology Sector 1 by facsimile transmission. Papers should be faxed to Crystal Mall 1, Art Unit 1638, using fax number (703) 308-4242. All Technology Sector 1 fax machines are available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Bui whose telephone number is (703) 305-1996.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Phuong Bui
Primary Examiner
Group Art Unit 1638
December 2, 2003



PHUONG T. BUI
PRIMARY EXAMINER